Published in final edited form as:

MAGMA. 2015 August ; 28(4): 407–412. doi:10.1007/s10334-014-0475-y.

Measurement reproducibility of magnetic resonance imaging-based finite element analysis of proximal femur microarchitecture for in vivo assessment of bone strength

Gregory Chang,

Department of Radiology, Center for Biomedical Imaging, NYU Langone Medical Center, 660 First Avenue, Room 334, 3rd Floor, New York, NY 10016, USA. Department of Radiology, Center for Biomedical Imaging, NYU Langone Medical Center, 660 First Avenue, 4th Floor, New York, NY 10016, USA

Alexandra Hotca-Cho,

Department of Radiology, Center for Biomedical Imaging, NYU Langone Medical Center, 660 First Avenue, 4th Floor, New York, NY 10016, USA

Henry Rusinek,

Department of Radiology, Center for Biomedical Imaging, NYU Langone Medical Center, 660 First Avenue, 4th Floor, New York, NY 10016, USA

Stephen Honig,

Osteoporosis Center, Hospital for Joint Diseases, NYU Langone Medical Center, 301 E. 17th Street, Suite 1101, New York, NY 10003, USA

Artem Mikheev,

Department of Radiology, Center for Biomedical Imaging, NYU Langone Medical Center, 660 First Avenue, 4th Floor, New York, NY 10016, USA

Kenneth Egol,

Department of Orthopaedic Surgery, Hospital for Joint Diseases, NYU Langone Medical Center, 301 E. 17th Street, 14th Floor, New York, NY 10003, USA

Ravinder R. Regatte, and

Department of Radiology, Center for Biomedical Imaging, NYU Langone Medical Center, 660 First Avenue, 4th Floor, New York, NY 10016, USA

Chamith S. Rajapakse

Department of Radiology, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA

Gregory Chang: Gregory.chang@nyumc.org

Correspondence to: Gregory Chang, Gregory.chang@nyumc.org.

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical standards This study had institutional review board approval and written informed consent was obtained from all subjects. Specifically, it was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All data were de-identified and this manuscript does not contain patient data.

Abstract

Introduction—Osteoporosis is a disease of weak bone. Our goal was to determine the measurement reproducibility of magnetic resonance assessment of proximal femur strength.

Methods—This study had institutional review board approval, and written informed consent was obtained from all subjects. We obtained images of proximal femur microarchitecture by scanning 12 subjects three times within 1 week at 3T using a high-resolution 3-D FLASH sequence. We applied finite element analysis to compute proximal femur stiffness and femoral neck elastic modulus.

Results—Within-day and between-day root-mean-square coefficients of variation and intraclass correlation coefficients ranged from 3.5 to 6.6 % and 0.96 to 0.98, respectively.

Conclusion—The measurement reproducibility of magnetic resonance assessment of proximal femur strength is suitable for clinical studies of disease progression or treatment response related to osteoporosis bone-strengthening interventions.

Keywords

Hip; Osteoporosis; MRI; Microarchitecture; Finite element analysis

Introduction

Osteoporosis is a disease of bone fragility caused by “low bone mass and microarchitectural deterioration of bone tissue,” leading to an increased risk of fracture [1]. Two million fractures occur in the United States annually, and of these, 300,000 occur in the hip or proximal femur [2]. The standard of care test for the diagnosis of osteoporosis is dual-energy X-ray absorptiometry (DXA) estimation of areal bone mineral density (BMD) in the proximal femur and lumbar spine. However, DXA does not assess bone microarchitecture, which is included in the World Health Organization (WHO) definition of osteoporosis. Furthermore, the majority of patients with fragility fractures do not even meet DXA criterion for an osteoporosis diagnosis (BMD T score <-2.5) [3].

Bone microarchitecture, which refers to the unique shape, arrangement, and geometry of bone tissue on the microstructural level, can be assessed noninvasively in vivo via high-resolution magnetic resonance imaging (MRI) [4, 5]. Many studies have shown the value of assessing morphologic and topologic parameters of bone microstructure (e.g., trabecular number, plate-to-rod ratio, and connectivity) for the improved detection of patients at risk for fracture and the more sensitive monitoring of disease progression and treatment response [5, 6]. In addition, finite element analysis (FEA), an engineering method, permits assessment of mechanical properties of bone microstructure in vivo [6]. This is highly appealing since osteoporosis is ultimately a disease of low bone strength.

Due to limitations in signal-to-noise ratio (SNR), MRI studies of bone microarchitecture have been performed almost exclusively in the distal radius or distal tibia, and not in the proximal femur, the most devastating site of fragility fracture. However, recently, in vivo imaging of proximal femur microarchitecture has become possible in vivo due to SNR gains

stemming from multichannel coils and SNR efficient pulse sequences [7, 8]. In one cross-sectional study, FEA applied to MR images of proximal femur microarchitecture detected lower bone strength in subjects with fragility fractures compared with control subjects who did not differ by BMD [9].

If a test is to be used clinically, its measurement precision must be determined. The goal of this study was to determine the measurement reproducibility for in vivo MRI-based FEA of proximal femur microarchitecture. This information is needed in order to calculate sample sizes for longitudinal studies of disease progression or response to therapy.

Materials and methods

Subject recruitment

This study had institutional review board approval and written informed consent was obtained from all subjects. From the Osteoporosis Center at our institution, we recruited 12 subjects without fracture (10 female, 2 male; mean age = 57.4 ± 13.6 years). The mean total hip BMD *T* score for subjects was -1.9 ± 0.8 and the mean femoral neck BMD *T* score for subjects was -2.3 ± 0.8 .

MRI scanning

The non-dominant proximal femur of each subject was scanned three times (twice on one day with repositioning between scans, and once 1 week later) on a 3T whole body MRI scanner (Siemens Skyra, Erlangen, Germany) using a 26 element receive-coil setup (18 elements from a body matrix coil anteriorly and eight elements from a spine coil posteriorly) [9]. The coil was wrapped around the hip and secured by sandbags laterally and a velcro strap. We used a 3-dimensional (3-D) fast low-angle shot sequence (FLASH) with the following scan parameters: repetition time (TR)/echo time (TE) = 37 ms/4.92 ms, 0.234 mm $\times$ 0.234 mm, slice thickness = 1.5 mm, 60 coronal slices, bandwidth = 200 Hz/pixel, parallel acceleration [generalized autocalibrating partially parallel acquisition (GRAPPA) factor = 2, and acquisition time = 15 min 18 s]. The imaging parameters were chosen in order to have the smallest voxel size possible while maintaining high enough SNR to visualize trabeculae and, most importantly, perform the image analysis (minimum of SNR $\sim$ 10–15 required [5]).

Segmentation of images and generation of a bone volume fraction map

Figure 1a illustrates the workflow for image analysis. First, under the guidance of a musculoskeletal radiologist, the whole proximal femur was segmented from surrounding soft tissues using in-house developed software (Firevoxel). Next, the grayscale values of the images were linearly scaled to cover the range from 0 % to 100 %, with pure marrow and bone intensity in the femur having minimum and maximum values, respectively [6]. This approach allows us to account for both partial volume effects and the presence of red marrow, which may have a different signal intensity than fatty marrow. We refer to the resulting 3-D array representing the fractional occupancy of bone at each voxel location as the bone-volume fraction (BVF) map.

Finite element analysis to compute whole proximal femur stiffness and femoral neck elastic modulus in a simulated sideways fall

We applied finite element analysis to MR images of proximal femur microarchitecture to assess metrics of bone strength [9]. Similar to BMD, which is assessed for the total hip and femoral neck, we assessed bone strength separately at the level of the whole proximal femur (bone stiffness) and for a $10 \times 10 \times 10 \text{ mm}^3$ volume of interest centered at the femoral neck (elastic modulus). In brief, each voxel from the selected BVF map (whole proximal femur or femoral neck volume of interest) was converted into a hexahedral finite element with dimensions corresponding to the voxel size. The material properties of bone were chosen as isotropic and linearly elastic with Young's modulus (YM) set to be linearly proportional to the BVF value such that $YM = 15 \text{ GPa} \times BVF$ while the Poisson's ratio was set at 0.3 for all elements. Since a sideways fall is the only fall characteristic that is associated with hip fracture [10], we performed simulated sideways loading along the bone's medial-lateral axis by applying a constant displacement ($\sim 1\%$ strain) to all finite element nodes of the femoral head in contact with the acetabulum while constraining those in the greater trochanter. The FE system was solved to yield a 3D strain map. Finally, whole proximal femur stiffness or femoral neck elastic modulus was obtained as the ratio of the resulting stress to the strain.

Statistical analysis

All statistical analysis was performed in SPSS v. 20 (IBM, Somers, New York). We computed the within-day and between-day root-mean-square coefficient of variation (RMS-CV), as well as the intraclass correlation coefficient (ICC) for whole proximal femur stiffness and femoral neck elastic modulus.

Results

Figure 1b shows MR images and strains maps (sideways fall) from three scans in one subject. Individual trabeculae are visible on images, and there is similar spatial variation in bone microarchitecture and strain on all three sets of images and maps.

FEA revealed the aggregate mean whole proximal femur stiffness for the 12 subjects to be $2.86 \pm 1.38 \text{ GPa}$ (Table 1). Plots of whole proximal femur stiffness for scans 1 and 2 (within-day scans) and scans 1 and 3 (between-day scans) are shown in Fig. 2a. The within-day RMS-CV for whole proximal femur stiffness was 4.8 %, and the ICC was 0.98 (0.91–0.98) (Table 1). The between-day RMS-CV for whole proximal femur stiffness was 5.2 %, and the ICC was 0.97 (0.89–1.00) (Table 1).

FEA revealed the mean femoral neck elastic modulus for the 12 subjects to be $4.69 \pm 2.09 \text{ GPa}$ (Table 1). Plots of femoral neck elastic modulus for scans 1 and 2 (within-day scans) and scans 1 scan 3 (between-day scans) are shown in Fig. 2b. The within-day RMS-CV for femoral neck elastic modulus was 3.5 %, and the ICC was 0.96 (0.88–0.99) (Table 1). The between-day RMS-CV for femoral neck elastic modulus was 6.6 %, and the ICC was 0.97 (0.90–0.99) (Table 1).

Discussion

We report the measurement reproducibility for MRI-based FEA of proximal femur microarchitecture to compute metrics of bone strength in vivo. The reproducibility is suitable for clinical longitudinal studies of disease progression or treatment response as outlined below. In addition, unlike FEA based on computed tomography (CT) images of the hip [11], this high-resolution MRI method permits visualization of individual trabeculae within the hip, and it does not administer ionizing radiation (safer for repeat scanning of the hip, which is close to radiosensitive organs in the pelvis). The proximal femur is an important osteoporotic fracture site, as proximal femur fractures result in high mortality in the first year after fracture and account for approximately 70 % (\$12 billion) of the direct annual costs in fracture care in the United States [2].

The motivation for using new methods to assess bone strength stems from limitations in DXA's ability to: (1) detect patients with skeletal fragility that are at risk for fracture and (2) monitor short-term changes in disease progression or treatment response. For example, most patients with osteoporotic fractures are misclassified by DXA as not osteoporotic [3]. In addition, after the start of antiresorptive therapy, BMD requires 1–2 years to change by only 0–4 %, and such small changes in BMD do not explain antifracture effects (up to 50 % lower fracture risk) [12]. DXA's low sensitivity for monitoring treatment response results in lengthy and expensive clinical trials [12]. In contrast, microarchitectural changes are detectable in vivo as early as 6–12 months in longitudinal disease progression [6] and treatment response studies [5].

The measurement reproducibility reported in this study is similar to that reported for MR-based FEA performed in the distal extremities. Within the distal radius and distal tibia, the coefficients of variation for MRI-based mechanical parameters were reported as 4 % [13] and less than 5 % [14], respectively. We believe that the reproducibility in our study was similarly high for a few reasons. First, there was little motion artifact on the images. This is likely because the hip is not mobile with the patient lying supine, and because we secured the coil with sandbags laterally and a Velcro strap. In the future, we could minimize motion artifact by implementing motion correction steps [5] or more SNR efficient pulse sequences (e.g., steady-state free precession and fast spin-echo [7]), which would permit reduced imaging time. Second, to minimize variation in image analysis, a musculoskeletal radiologist oversaw the segmentation of the whole proximal femur and femoral neck volumes of interest. We do note that our between-day reproducibility was slightly higher than the within-day reproducibility. This is probably due to small differences in patient positioning. In the future, atlas-based segmentation/registration could improve the reproducibility further [15]; this strategy has been successfully used in the neuroimaging community over the last 15 years.

Establishment of the reproducibility of this method is necessary to determine sample sizes for longitudinal studies of response to therapy. For example, given the CV of 5.6 % for whole proximal femur stiffness in this study, a clinical trialist would need to scan ten subjects before and after treatment with a bone-strengthening intervention to detect a 5.6 % improvement in proximal femur stiffness with 80 % power at the 5 % significance level. If

the CV were 11.2 % (twice as high), the clinical trialist would require 34 subjects scanned before and after treatment to detect a 5.6 % increase in proximal femur stiffness with 80 % power at the 5 % significance level. Overall, the CVs that we report in this study are suitable for longitudinal studies of disease progression or response to therapy.

This study has limitations. First, the voxel size is larger than that obtained when performing high-resolution MRI of the distal extremities. This is because the SNR achievable when imaging deep anatomy such as the hip (6–10 cm from the skin surface) is lower than the SNR achievable when imaging the distal radius/tibia, which are relatively superficial (1–3 cm from the skin surface) and close to the radiofrequency coil. Nevertheless, because of the higher SNR permitted by multielement receive arrays, including the receive setup used in this study [8], the resolution achieved is still sufficient to depict individual trabeculae. We also note that the resolution for in vivo MRI-based FEA is still higher than that achievable with CT-based FEA (0.674–1.08 mm in-plane, 3 mm slice thickness [11]), which also exposes the patient to ionizing radiation. Second, we note that the FE solver used in this study was developed in-house. However, FEA software is widely used in the mechanical engineering industry and is commercially available for purchase. Third, we note that the scan time was relatively long, which increases the chance for motion artifact, especially when imaging at high-resolution. As stated above, the implementation of motion correction steps [5] and more SNR efficient pulse sequences with shorter scan times [7] should help reduce these artifacts. Finally, regarding the FEA, we made assumptions for the Young's modulus, and Poisson ratio for the proximal femur, and isotropic elements, rather than anisotropic elements, would have been ideal. However, we note that the values chosen were based on values from the literature. In addition, low resolution, CT-based continuum FEA of the proximal femur with anisotropic voxels (0.674–1.08 mm in-plane, 3 mm slice thickness) has been shown in vitro to correlate strongly with bone strength computations derived from the gold standard of mechanical testing [11]. In the future, it will be important to compare MRI-based predictions of bone strength with CT-based predictions of bone strength.

Conclusion

In conclusion, we report the high measurement reproducibility for in vivo MRI-based FEA of proximal femur microarchitecture. This method can be performed using a commercially available coil and product sequence. The reproducibility is suitable for in vivo studies and will allow clinicians to determine sample sizes for longitudinal studies of disease progression or response to treatment.

Acknowledgments

This study was supported by United States National Institutes of Health K23 AR059748 (G.C.), RO1 AR066008 (G.C.), and K25 AR060283 (C.R.).

References

1. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet*. 2002; 359:1929–1936. [PubMed: 12057569]

2. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res.* 2007; 22:465–475. [PubMed: 17144789]
3. Schuit SC, van der Klift M, Weel AE, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone.* 2004; 34:195–202. [PubMed: 14751578]
4. Majumdar S. Magnetic resonance imaging of trabecular bone structure. *Top Magn Reson Imaging.* 2002; 13:323–334. [PubMed: 12464745]
5. Wehrli FW. Structural and functional assessment of trabecular and cortical bone by micro magnetic resonance imaging. *J Magn Reson Imaging.* 2007; 25:390–409. [PubMed: 17260403]
6. Rajapakse CS, Leonard MB, Bhagat YA, Sun W, Magland JF, Wehrli FW. Micro-MR imaging–based computational biomechanics demonstrates reduction in cortical and trabecular bone strength after renal transplantation. *Radiology.* 2012; 262:921–931. [PubMed: 22267587]
7. Han M, Chiba K, Banerjee S, Carballido-Gamio J, Krug R. Variable flip angle three-dimensional fast spin-echo sequence combined with outer volume suppression for imaging trabecular bone structure of the proximal femur. *J Magn Reson Imaging.* 2014; 1002/jmri.24673
8. Chang G, Deniz CM, Honig S, et al. Feasibility of three-dimensional MRI of proximal femur microarchitecture at 3 tesla using 26 receive elements without and with parallel imaging. *J Magn Reson Imaging.* 2014; 40:229–238. [PubMed: 24711013]
9. Chang G, Honig S, Brown R, et al. Finite element analysis applied to 3-T MR imaging of proximal femur microarchitecture: lower bone strength in patients with fragility fractures compared with control subjects. *Radiology.* 2014; 272:464–474. [PubMed: 24689884]
10. Greenspan SL, Myers ER, Maitland LA, Resnick NM, Hayes WC. Fall severity and bone mineral density as risk factors for hip fracture in ambulatory elderly. *JAMA.* 1994; 271:128–133. [PubMed: 8264067]
11. Keyak JH, Kaneko TS, Tehranzadeh J, Skinner HB. Predicting proximal femoral strength using structural engineering models. *Clin Orthop Relat Res.* 2005; 437:219–228. [PubMed: 16056052]
12. Seeman E. Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? *Bone.* 2007; 41:308–317. [PubMed: 17644058]
13. Lam SC, Wald MJ, Rajapakse CS, Liu Y, Saha PK, Wehrli FW. Performance of the MRI-based virtual bone biopsy in the distal radius: serial reproducibility and reliability of structural and mechanical parameters in women representative of osteoporosis study populations. *Bone.* 2011; 49:895–903. [PubMed: 21784189]
14. Bhagat YA, Rajapakse CS, Magland JF, et al. Performance of μ MRI-based virtual bone biopsy for structural and mechanical analysis at the distal tibia at 7T field strength. *J Magn Reson Imaging.* 2011; 33:372–381. [PubMed: 21274979]
15. Carballido-Gamio J, Folkesson J, Karampinos DC, et al. Generation of an atlas of the proximal femur and its application to trabecular bone analysis. *Magn Reson Med.* 2011; 66:1181–1191. [PubMed: 21432904]

Fig. 1.

a The image analysis workflow: (1) MRI scanning; (2) generation of bone volume fraction map; (3) performance of FEA to compute whole proximal femur stiffness and femoral neck elastic modulus. **b** Three representative MR images (*top row*) and corresponding microstructural strain maps (*bottom row*) from one subject. Scanning was performed twice on 1 day (with repositioning between scans) and once 1 week later

Fig. 2.

a Scan-rescan plots for the 12 subjects for scans 1 and 2 (within-day) and scans 1 and 3 (between-day) for whole proximal femur stiffness (**a**) and femoral neck elastic modulus (**b**)

Table 1

Aggregate mean, and within-day, and between-day root-mean-square coefficients of variation (RMS-CV) and intraclass correlation coefficients (ICC) with confidence intervals for whole proximal femur stiffness and femoral neck elastic modulus

	Whole proximal femur stiffness	Femoral neck elastic modulus
Aggregate Mean	2.86 ± 1.38 GPa	4.69 ± 2.09 GPa
Within-day RMS-CV	4.8 %	3.5 %
Within-day ICC	0.98 (0.91–0.98)	0.96 (0.88–0.99)
Between-day RMS-CV	5.2 %	6.6 %
Between-day ICC	0.97 (0.89–1.00)	0.97 (0.90–0.99)